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Multiple, Small Dose Administration of (-)Deprenyl Enhances Catecholaminergic Activity and Diminishes Serotoninergic Activity in the Brain and these Effects Are Unrelated to MAO-B Inhibition

J. KNOLL AND I. MIKLYA

Department of Pharmacology, Semmelweis University of Medicine, Nagyvárad tér 4, P.O.B. 370, H-1445 Budapest, Hungary

Abstract—As a measure of the basic activity of the catecholaminergic and serotoninergic systems, the biogenic amines released from freshly excised brain tissue were measured by means of HPLC with electrochemical detection. Rats of both sexes were injected subcutaneously, daily for 21 days, either with saline or with a dose of one of the enantiomers of the following compounds: deprenyl; *p*-fluorodeprenyl; 1-phenyl-2-propylaminopentane, a deprenyl analogue free of MAO-B inhibitory potency; methamphetamine, the parent compound of deprenyl; and amphetamine, the parent compound of 1-phenyl-2-propylaminopentane. The release of the biogenic amines from brain tissue was measured 24 hours after the last injection.

The effect of the two enantiomers of deprenyl was studied in five doses (0.01, 0.025, 0.05, 0.1 and 0.25 mg/kg), that of (−)1-phenyl-2-propylaminopentane in two doses (0.05 and 0.1 mg/kg), others in 0.05 mg/kg. Treatment with (−)deprenyl enhanced the release of dopamine from striatum, substantia nigra and tuberculum olfactorium (significant in 0.01–0.25 mg/kg) and the release of noradrenaline from the locus coeruleus (significant in 0.05–0.25 mg/kg), whilst the release of serotonin from the raphe was diminished (significant in 0.05–0.25 mg/kg in males and 0.25 mg/kg in females). (+)Deprenyl was slightly less potent than (−)deprenyl.

Both *p*-fluorodeprenyl and 1-phenyl-2-propylaminopentane acted like deprenyl; the (+)enantiomers were more active than the (−)forms. (−)Methamphetamine was as potent as (−)deprenyl in enhancing the catecholaminergic activity and more potent than (−)deprenyl in diminishing the serotoninergic activity. (+)Methamphetamine was substantially less potent than (−)methamphetamine.

(−)Amphetamine was as potent as (−)methamphetamine and (+)amphetamine was more potent than (+)methamphetamine in enhancing the catecholaminergic activity but neither (−)amphetamine nor (+)amphetamine diminished the serotoninergic activity.

On the one hand, the results prove that the described effects of deprenyl are unrelated to MAO-B inhibition, on the other hand, they indicate the existence of hitherto unknown catecholaminergic and serotoninergic activity enhancer mechanisms in the brain, of which the former is stimulated and the latter inhibited by multiple, small dose administrations of deprenyl and related substances.

Introduction

(−)Deprenyl, developed as a new spectrum psychoenergizer (Knoll *et al.*, 1965), unique in being free of the "cheese effect" (Knoll *et al.*, 1968), became the first selective inhibitor of B-type MAO described in the literature (Knoll and Magyar, 1972) and is still the only one used in clinical practice. According to the generally accepted view, the beneficial effects of (−)deprenyl in Parkinson's disease and in Alzheimer's disease are due to the selective inhibition of MAO-B in the brain (cf Szelényi, 1993).

Rats treated during the postdevelopmental phase of life with 0.25 mg/kg of (−)deprenyl, s.c., 3 times a week until death, perform better in behavioral test, have a slower age-related decline in sexual and learning performance and live longer than their saline-treated peers (Knoll, 1985, 1988; Knoll *et al.*, 1989). Our finding that (−)deprenyl medication prolongs the life of rats has been confirmed by others (Milgram *et al.*, 1990; Kitani *et al.*, 1992).

It has been demonstrated that (−)deprenyl protects nigrostriatal dopaminergic neurons. Treatment of rats with this drug for 18 months prevented characteristic age-related structural changes of melanin granules in the neurocytes of the substantia nigra (Knoll *et al.*, 1992a). Single dose administration of the drug prevented the neurotoxic effect of 6-hydroxydopamine by inhibiting its neuronal uptake (Knoll, 1978, Hársing *et al.*, 1979). (−)Deprenyl inhibits MAO-B, which catalyzes the conversion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to its toxic metabolite 1-methyl-4-phenyl-pyridinium ion (MPP^+) (Cohen *et al.*, 1984), and also has a protective effect against MPP^+ (Vizuete *et al.*, 1993; Wu *et al.*, 1993).

Recent studies suggest that enhanced catecholaminergic activity in the brain, unrelated to the selective inhibition of MAO-B, is the cause of the

peculiar behavioral effects of long-lasting, small dose administration of (−)deprenyl in the rat, and probably in man too (Knoll, 1992a, 1992b, 1992c; 1993a, 1993b, 1993c). Patients with a long history of Parkinson's disease lived longer when levodopa was given together with 10 mg of (−)deprenyl daily (Birkmayer *et al.*, 1985); other patients treated with 10 mg of (−)deprenyl daily alone, needed levodopa significantly later than their untreated peers (Tetrud and Langston, 1989; Parkinson Study Group, 1989, 1993).

An analysis of the mechanism of action of the central nervous system effects of (−)deprenyl unrelated to MAO inhibition is the aim of this paper.

Methods

Selection of animals and their treatment

We started the experiments with Wistar rats of both sexes which completed their 2nd month of life. The rats were fed with standard diet and water *ad libitum*. We treated them either with 0.9% NaCl (0.3 ml/100 g) or with a dose of one of the enantiomers of the following compounds: amphetamine (A), methamphetamine (MA), deprenyl (D), *p*-fluorodeprenyl (pFD), 1-phenyl-2-propylaminopentane (PPAP), dissolved in 0.9% NaCl. The volume injected s.c. was 0.3 ml/100 g. The rats were injected once a day for 21 days and the brain samples, for measuring the release of the biogenic amines, were removed 24 hr after the last injection.

Measurement of the release of dopamine, noradrenaline and serotonin from proper brain areas

Rats were decapitated and appropriate brain samples were quickly removed and soaked in carbogenated Krebs solution. After incubation of the tissue for 20 min, the Krebs solution was replaced, the tissue soaked for 20 min in fresh Krebs solution and the amount of biogenic amine released during this period of time estimated. Samples were purified on 90 mg alumina-containing microcolumns according to the method of Anton and Sayre (1962).

We measured the release of dopamine from the striatum, substantia nigra and tuberculum olfactorium, of noradrenaline from the locus coeruleus and of serotonin from the raphe. Dopamine, noradrenaline and serotonin were determined by HPLC with electrochemical detection. The appropriate amine was used as control. Details of chromatography are described in a previous paper (Kerecsen *et al.*, 1986). The instrumental assembly for measuring the biogenic amines consisted of a Waters pump 510, a Waters U6K injector, a Waters 460 electrochemical detector and a

Waters 746 data module (Millipore Corp., Waters Chromatography Division, Bedford, MA, U.S.A.). For statistical evaluations, the Student's *t*-test for two means was applied. The significance level was set at $p < 0.05$.

Results

In both males (Table I) and females (Table II), treatment with (−)deprenyl enhanced the release of dopamine from the striatum, substantia nigra and tuberculum olfactorium (significant in 0.01–0.25 mg/kg) and of noradrenaline from the locus coeruleus (significant in 0.05–0.25 mg/kg), whilst the release of serotonin from the raphe was diminished (significant in 0.05–0.25 mg/kg in males and in 0.25 mg/kg in females). (+)Deprenyl was slightly less potent than (−)deprenyl (Tables III and IV). The lowest dose of (+)deprenyl (0.01 mg/kg) increased the release of serotonin significantly.

Though pFD has the same pharmacological profile as deprenyl, being a highly potent inhibitor of MAO-B and of the uptake of tyramine, we found a remarkable difference between the effects of the enantiomers of deprenyl and pFD in this test. In both males and females, (+)pFD was much more potent than (−)pFD in enhancing the catecholaminergic activity. These differences clearly indicate that the effects of deprenyl and pFD, described in this paper, are unrelated to MAO inhibition.

PPAP, a deprenyl analogue free of MAO inhibitory potency but otherwise possessing the same pharmacological spectrum as deprenyl (Knoll *et al.*, 1992b), acted essentially similarly to deprenyl (Tables V-VIII). (+)PPAP (0.05 mg/kg) significantly enhanced the catecholaminergic activity in both males and females and significantly diminished the serotoninergic activity in males (Tables VII-VIII). (−)PPAP, the effect of which was studied in two doses (0.05 and 0.1 mg/kg), significantly increased the release of noradrenaline in males, whereas the serotoninergic activity was significantly decreased in the lower dose (Table V). In females too, (−)PPAP enhanced the release of noradrenaline in both doses but had no significant effect on the release of serotonin. The serotoninergic activity showed a tendency to decline, although the change remained statistically insignificant (Table VI). The results with PPAP furnish prima-facie evidence that the effects of (−)deprenyl, shown in Tables I-IV, are unrelated to MAO-B inhibition.

Amphetamine, the parent compound of PPAP, exerts its acute psychostimulant effects in doses higher than 0.5 mg/kg. It enhanced in our test the catecholaminergic activity in a dose of 0.05 mg/kg (Tables V-VIII), which is completely ineffective in behavioral tests.

(−)Methamphetamine, the parent compound of (−)deprenyl, enhanced both dopaminergic and noradrenergic activity, similarly to (−)deprenyl.

TABLE I

Release of biogenic amines from brain samples of male rats treated with (−)deprenyl daily for 21 days

Treatment	Daily dose (mg/kg)	Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
		Dopamine			Noradrenaline	Serotonin
		Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Saline	–	2.72 ± 0.10	2.96 ± 0.13	2.58 ± 0.06	4.10 ± 0.18	0.461 ± 0.01
(−)Deprenyl	0.01	3.27 ± 0.14***	4.17 ± 0.31****	3.08 ± 0.18***	6.13 ± 0.62***	0.519 ± 0.05
	0.025	3.62 ± 0.11****	3.48 ± 0.15*	3.63 ± 0.13****	4.53 ± 0.27	0.450 ± 0.02
	0.05	4.42 ± 0.09****	4.47 ± 0.09****	4.53 ± 0.33****	7.88 ± 0.23****	0.357 ± 0.04**
	0.10	4.75 ± 0.20****	4.73 ± 0.16****	4.15 ± 0.13****	7.13 ± 0.58****	0.354 ± 0.02****
	0.25	5.70 ± 0.13****	7.71 ± 0.06****	4.55 ± 0.12****	9.32 ± 0.47****	0.209 ± 0.01****

Values are means ± S.E.M.; n = 12.
*p < 0.05; **p < 0.02; ***p < 0.01; ****p < 0.001.

TABLE II

Release of biogenic amines from brain samples of female rats treated with (−)deprenyl daily for 21 days

Treatment	Daily dose (mg/kg)	Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
		Dopamine			Noradrenaline	Serotonin
		Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Saline	–	2.42 ± 0.06	2.80 ± 0.03	2.42 ± 0.1	3.67 ± 0.23	0.460 ± 0.03
(−)Deprenyl	0.01	3.20 ± 0.08***	3.18 ± 0.07***	3.37 ± 0.09***	3.97 ± 0.23	0.444 ± 0.02
	0.025	3.62 ± 0.11***	3.48 ± 0.15*	3.63 ± 0.13***	4.53 ± 0.27	0.450 ± 0.02
	0.05	3.73 ± 0.27***	3.55 ± 0.19***	3.35 ± 0.18***	7.70 ± 0.10***	0.370 ± 0.04
	0.10	4.68 ± 0.12***	4.50 ± 0.07***	4.60 ± 0.18***	7.07 ± 0.12***	0.360 ± 0.02
	0.25	4.32 ± 0.07***	5.15 ± 0.12***	4.48 ± 0.23***	5.10 ± 0.10***	0.280 ± 0.01**

Values are means ± S.E.M.; n = 12.
*p < 0.05; **p < 0.01; ***p < 0.001.

TABLE III

Release of biogenic amines from brain samples of male rats treated with (+)deprenyl daily for 21 days

Treatment	Daily dose (mg/kg)	Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
		Dopamine			Noradrenaline	Serotonin
		Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Saline	–	2.72 ± 0.10	2.96 ± 0.13	2.58 ± 0.06	4.10 ± 0.18	0.461 ± 0.01
(+)Deprenyl	0.01	2.90 ± 0.08	4.50 ± 0.32****	2.08 ± 0.13	4.40 ± 0.06	0.508 ± 0.01**
	0.025	3.60 ± 0.15****	4.00 ± 0.23****	3.50 ± 0.23****	5.00 ± 0.21**	0.476 ± 0.03
	0.05	3.30 ± 0.32*	3.20 ± 0.13	3.30 ± 0.29***	7.80 ± 0.54****	0.499 ± 0.01
	0.10	4.90 ± 0.16****	5.30 ± 0.09****	6.10 ± 0.08****	7.80 ± 0.09****	0.356 ± 0.02**
	0.25	5.20 ± 0.12****	8.60 ± 0.23****	5.10 ± 0.08****	8.80 ± 0.23****	0.229 ± 0.01****

Values are means ± S.E.M.; n = 12.
*$p < 0.05$; **$p < 0.02$; ***$p < 0.01$; ****$p < 0.001$.

TABLE IV

Release of biogenic amines from brain samples of female rats treated with (+)deprenyl daily for 21 days

Treatment	Daily dose (mg/kg)	Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
		Dopamine			Noradrenaline	Serotonin
		Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Saline	–	2.42 ± 0.06	2.80 ± 0.03	2.42 ± 0.1	3.67 ± 0.23	0.460 ± 0.03
(+)Deprenyl	0.01	2.93 ± 0.08	2.87 ± 0.16****	2.75 ± 0.13	4.40 ± 0.06	0.508 ± 0.01**
	0.025	3.18 ± 0.06****	3.88 ± 0.13***	3.18 ± 0.08****	5.00 ± 0.21**	0.476 ± 0.03
	0.05	3.62 ± 0.17****	3.63 ± 0.20****	3.75 ± 0.19****	7.90 ± 0.16****	0.470 ± 0.01
	0.10	4.50 ± 0.28****	5.68 ± 0.19****	4.62 ± 0.11****	4.70 ± 0.40*	0.370 ± 0.02
	0.25	3.88 ± 0.10****	4.42 ± 0.11****	4.25 ± 0.16****	7.37 ± 0.27****	0.260 ± 0.03**

Values are means ± S.E.M.; n = 12.
*p < 0.05; **p < 0.02; ***p < 0.01; ****p < 0.001.

TABLE V

Release of biogenic amines from brain samples of male rats treated with (−)amphetamine (A), (−)methamphetamine (MA), (−)1-phenyl-2-propylaminopentane (PPAP) and (−)p-fluorodeprenyl (pFD) daily for 21 days

Treatment	Daily dose (mg/kg)	Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
		Dopamine			Noradrenaline	Serotonin
		Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Saline	–	2.72 ± 0.10	2.96 ± 0.13	2.58 ± 0.06	4.10 ± 0.18	0.461 ± 0.01
(−)A	0.05	4.30 ± 0.34****	4.80 ± 0.18****	3.60 ± 0.80	5.00 ± 0.40*	0.613 ± 0.07 **
(−)MA	0.05	3.77 ± 0.08****	3.53 ± 0.23*	3.65 ± 0.19****	6.20 ± 0.26****	0.214 ± 0.002****
(−)PPAP	0.05	2.02 ± 0.21***	2.15 ± 0.35**	1.92 ± 0.23***	5.03 ± 0.18**	0.310 ± 0.04 ****
	0.10	5.17 ± 0.29****	4.52 ± 0.46****	5.02 ± 0.21***	7.93 ± 0.69****	0.466 ± 0.03
(−)pFD	0.05	2.60 ± 0.26	2.70 ± 0.15	2.40 ± 0.19	3.60 ± 0.19	0.295 ± 0.03 ****

Values are means ± S.E.M.; n = 12.
*$p < 0.05$; **$p < 0.02$; ***$p < 0.01$; ****$p < 0.001$.

TABLE VI

Release of biogenic amines from brain samples of female rats treated with (−)amphetamine (A), (−)methamphetamine (MA), (−)1-phenyl-2-propylaminopentane (PPAP) and (−)p-fluorodeprenyl (pFD) daily for 21 days

		Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
		Dopamine			Noradrenaline	Serotonin
Treatment	Daily dose (mg/kg)	Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Saline	–	2.42 ± 0.06	2.80 ± 0.08	2.42 ± 0.10	3.67 ± 0.14	0.460 ± 0.03
(−)A	0.05	3.65 ± 0.18****	4.02 ± 0.16****	3.97 ± 0.23	4.39 ± 0.23*	0.570 ± 0.04
(−)MA	0.05	2.87 ± 0.14***	3.62 ± 0.10****	2.85 ± 0.11**	5.23 ± 0.52***	0.300 ± 0.04**
(−)PPAP	0.05	2.58 ± 0.12	2.87 ± 0.15	2.72 ± 0.15	4.77 ± 0.38**	0.340 ± 0.04
	0.10	4.90 ± 0.26****	5.65 ± 0.26****	5.02 ± 0.21****	7.93 ± 0.69****	0.390 ± 0.01
(−)pFD	0.05	3.42 ± 0.48**	2.52 ± 0.24	2.25 ± 0.24	4.00 ± 0.12	0.450 ± 0.05

Values are means ± S.E.M.; n = 12.
*p < 0.05; **p < 0.02; ***p < 0.01; ****p < 0.001.

TABLE VII

Release of biogenic amines from brain samples of male rats treated with (+)amphetamine (A), (+)methamphetamine (MA), (+)1-phenyl-2-propylaminopentane (PPAP) and (+)p-fluorodeprenyl (pFD) daily for 21 days

Treatment	Daily dose (mg/kg)	Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
		Dopamine			Noradrenaline	Serotonin
		Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Saline	–	2.72 ± 0.10	2.96 ± 0.13	2.58 ± 0.06	4.10 ± 0.18	0.461 ± 0.01
(+)A	0.05	4.20 ± 0.20**	4.60 ± 0.23**	3.80 ± 0.23**	4.10 ± 0.35	0.532 ± 0.07
(+)MA	0.05	2.90 ± 0.17	3.90 ± 0.41*	3.00 ± 0.24	3.70 ± 0.27	0.595 ± 0.02**
(+)PPAP	0.05	4.50 ± 0.27**	4.10 ± 0.21**	3.60 ± 0.42*	9.00 ± 0.62**	0.350 ± 0.02*
(+)pFD	0.05	4.30 ± 0.44**	4.90 ± 0.36**	4.00 ± 0.26**	9.00 ± 0.52**	0.455 ± 0.07

Values are means ± S.E.M.; n = 12.
*$p < 0.01$; **$p < 0.001$.

TABLE VIII

Release of biogenic amines from brain samples of female rats treated with (+)amphetamine (A), (+)methamphetamine (MA), (+)1-phenyl-2-propylaminopentane (PPAP) and (+)p-fluorodeprenyl (pFD) daily for 21 days

		Amount of biogenic amine (nmoles/g tissue) released from the tissue within 20 min				
		Dopamine			Noradrenaline	Serotonin
Treatment	Daily dose (mg/kg)	Striatum	Substantia nigra	Tuberculum olfactorium	Locus coeruleus	Raphe
Saline	–	2.42 ± 0.06	2.80 ± 0.08	2.42 ± 0.10	3.67 ± 0.14	0.460 ± 0.03
(+)A	0.05	3.93 ± 0.22**	4.17 ± 0.30**	3.60 ± 0.26**	5.00 ± 0.35*	0.470 ± 0.07
(+)MA	0.05	2.93 ± 0.17*	2.72 ± 0.19	2.65 ± 0.18	3.90 ± 0.20	0.480 ± 0.03
(+)PPAP	0.05	3.88 ± 0.32**	4.00 ± 0.25**	3.63 ± 0.19**	4.23 ± 0.12*	0.410 ± 0.02
(+)pFD	0.05	5.02 ± 0.36**	6.77 ± 0.45**	4.53 ± 0.35**	4.70 ± 0.12*	0.490 ± 0.04

Values are means ± S.E.M.; n = 12.
*$p < 0.01$; **$p < 0.001$.

The (+)enantiomer of methamphetamine was significantly less potent than the (−)form (Tables V-VIII). (−)Methamphetamine diminished the serotoninergic activity in both sexes, whereas (+)methamphetamine was ineffective in females and even increased the serotonin release in males (Table VII).

Discussion

The data prove that repeated administration of much smaller doses of (−)deprenyl than the usually used one (0.25 mg/kg), which blocks completely MAO-B activity, enhances significantly the release of catecholamines and diminishes the release of serotonin in the brain. The finding that also multiple, small dose administration of (−)PPAP and (−)methamphetamine acts similarly, furnishes direct evidence that these effects of (−)deprenyl are unrelated to the inhibition of MAO-B.

(−)Methamphetamine, the parent compound of deprenyl, enhanced the catecholaminergic activity and diminished the serotoninergic activity similarly to deprenyl. The low dose of (−)methamphetamine (0.05 mg/kg), used in the present study, did not exert significant effects in the battery of behavioral tests we generally use for measuring psychostimulant activities (cf Knoll *et al.*, 1992b). Indeed, this dose of (−)methamphetamine did not change the spontaneous motility in the shuttle box, did not increase locomotion and the number of rearings and did not generate stereotyped head movements in the "Animal Activity Measurement System", did not change the excitability of the central nervous system as measured in the "modified jumping test" and did not change learning and retention in the shuttle box. The threshold dose of (−)methamphetamine which exerted significant changes in these tests, was found to be higher than 0.5 mg/kg.

With regard to the mechanism of action of the low dose effects of (−)deprenyl and related substances, we assume that hitherto unknown catecholaminergic and serotoninergic activity enhancer mechanisms exist in the brain, of which the former is stimulated and the latter inhibited by multiple, small dose administrations of deprenyl, its parent compound, methamphetamine, and their structural relatives. The exact nature of the catecholaminergic and serotoninergic enhancer mechanisms in the brain influenced by multiple, low dose administrations of (−)deprenyl is now the subject of experiments in progress.

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